Table 1 - 90% CI for Chlorthalidone

Condition	AUC	logAUC	CMAX	logCMAX
1[a,b]	(b)4 - Confidential Business			
2[b]				
3[a,b]				
4[b]				
5[a,b]				
6[a,b]				

Condition:

1 Sponsor's originally reported data (all subjects)

2 Condition 1 without Subject 5

3 Revised data calculated by reviewer (all subjects) (Standard curves ANQ03 and ANQ05 recalculated)

4 Condition 3 without Subject 5

5 Condition 3 without Subjects 5 and 6

6 Condition 3 using only levels > 500 for Subjects 5, 6, and 7

[a] Statistically significant ($p < 0.1$) sequence effect for all parameters

[b] Statistically significant ($p < 0.05$) treatment effect for all parameters

Table 2 - Nonlinear Regression Analysis of Chlorthalidone Data

Sub. Trt	KEL (hr^{-1})	$t_{\frac{1}{2}}$ (hr)	AUC_{∞} (mg-hr/L)	NUM-HALF	AUC_{t} (mg-hr/L)	RATIO	WASHOUT (# $t_{\frac{1}{2}}$)
1,1							
2,1							
3,1							
4,1							
5,1							
6,1							
7,1							
8,1							
9,1							
10,1							
11,1							
12,1							
14,1							
15,1							
16,1							
17,1							
18,1							
19,1							
20,1							
21,1							
22,1							
23,1							
24,1							
25,1							
Mean	.01443	49.31	165.9828	2.5	134.6163	.819	7.12
CV %	16.19	16.95	23.18	16.2	18.48	6.24	14.7
MIN.	.01041	36.52	87.462	1.8	79.351	.720	5.85
MAX.	.01898	66.58	287.652	3.3	208.52	.907	9.20

(b)4 - Confidential Business

1,2	[redacted]						
2,2							
3,2							
4,2							
5,2							
6,2							
7,2							
8,2							
9,2							
10,2							
11,2							
12,2							
14,2							
15,2							
16,2							
17,2							
18,2							
19,2							
20,2							
21,2							
22,2							
23,2							
24,2							
25,2							
Mean	.01418	50.36	160.0012	2.43	128.4323	.809	6.83
CV %	17.2	18.12	22.15	17.7	19.42	6.93	16.0
MIN.	.0092	35.51	90.167	1.6	79.362	.6874	5.28
MAX.	.0195	75.02	255.99	3.38	190.593	.9167	8.59

NUMHALF = t_{LAST} / $t_{1/2}$
RATIO = AUC_{0-t} / $AUC_{0-\infty}$
WASHOUT = 336 / $t_{1/2}$

Table 3 - Extrapolated Chlorthalidone Concentrations from Period 1

Subj.	CLAST1 (ng/ml)	KE-Sponsor (1/hr)	CPRR2-Sponsor (ng/ml)	KE-Reviewer (1/hr)	CPRR2-Reviewer (ng/ml)
1	507.5	.014	24.67	.01322	29.19
2	533.2	.013	32.17	.01262	34.92
5	151.3	.02	2.01	.01898	2.51
6	613.7	.013	37.02	.01288	37.99
10	520.8	.013	31.42	.0127	33.52
14	536.6	.013	32.37	.01285	33.44
16	423.3	.013	25.54	.01203	31.49
17	439.7	.014	21.37	.01444	19.43
21	384.4	.013	23.19	.01282	24.11
23	606	.011	56.31	.0109	57.54
25	394.9	.015	15.47	.01478	16.22

Table 4 - T/R Ratios (%) for Atenolol

Subject	AUC_{0-t}	$AUC_{0-\infty}$	C_{max}
1	68.6	70.6	77.6
2	71.7	74.0	67.5
3	116.4	115.7	104.4
4	82.4	81.5	87.0
5	99.2	100.5	86.5
6	78.1	78.5	61.9
7	94.2	95.1	86.9
8	88.1	90.3	74.6
9	136.6	131.1	173.1
10	94.8	93.8	105.6
11	85.1	88.2	110.0
12	78.6	79.7	78.4
14	88.5	91.0	84.7
15	101.5	102.5	97.3
16	81.2	83.4	74.6
17	150.7	142.1	151.6
18	76.4	77.0	75.5
19	106.4	106.6	103.8
20	87.6	87.2	102.4
21	121.4	118.4	100.3
22	157.3	150.3	158.4
23	62.5	63.8	67.0
24	77.6	75.2	82.3
25	79.8	80.9	62.6
> 125%	3	3	3
75.0-125.0%	18	18	15
< 75%	3	3	6

Table 5 - T/R Ratios (%) for Chlorthalidone

Subject	AUC_t	AUC_∞	C_{max}
1	89.9	89.0	94.3
2	104.4	105.3	103.7
3	124.7	115.2	129.7
4	103.1	100.6	100.2
5	93.9	93.3	97.9
6	97.7	100.5	103.5
7	99.2	99.9	99.6
8	101.0	95.5	117.0
9	109.4	109.2	105.9
10	102.2	102.6	98.5
11	103.9	102.6	100.5
12	84.7	82.3	90.9
14	104.5	103.5	105.9
15	124.0	113.6	110.1
16	117.2	125.2	116.3
17	108.7	105.9	117.7
18	105.9	104.0	111.8
19	112.4	111.3	113.2
20	92.9	93.0	97.3
21	99.3	97.4	103.2
22	141.7	142.0	142.0
23	98.9	93.8	103.8
24	108.4	104.2	100.0
25	108.5	107.8	104.7
> 125%	1	2	2
75.0-125.0%	23	22	22
< 75%	0	0	0

Table 6 - Corrected Values for Revised Atenolol Data

	Trt. A (test)		Trt. B (ref.)		% Diff.	90% CI
	Mean	CV(%)	Mean	CV(%)		
$AUC_{0-\infty}$ (ng-hr/ml)	5513.97	29.45	6021.51	32.38	-8.43	85.5-97.6
log$AUC_{0-\infty}$	-	-	-	-	-	86.5-100.1
RATIO (range)	0.9091 [redacted]	4.43	0.9128 [redacted]	4.2	-0.41	-
KEL (hr^{-1})	0.1085	18.88	0.1135	15.41	-3.7	-
$T_{1/2}$ (hr)	6.729	30.11	6.37	24.98	5.64	-
NUMHALF (range)	3.67 [redacted]	15.78	3.76 [redacted]	15.84	-2.39	-

Trt. A = Atenolol/Chlorthalidone 100/25 mg (Sidmak)
Trt. B = Tenoretic® 100/25 mg (ICI)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-107 **SPONSOR:** Sidmak Laboratories

DRUG: atenolol/chlorthalidone

DOSAGE FORM: tablet

STRENGTHS/(s): 100/25 mg and 50/25 mg

TYPE OF STUDY: Single X Multiple __ Fasting X Fed

STUDY SITE: (b)4 - Confidential Business

STUDY SUMMARY: 25/26 healthy male subjects completed, data analyzed from first 12 subjects in each sequence, randomized, single dose (100/25 mg), two way crossover design, 14-day washout. For both components, reported 90% CI for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were within the acceptable 80-120% range (untransformed). After data revisions (recalculation of some standard curves and kel values), the 90% CI for revised data for both components were all within the allowed equivalence intervals for both untransformed and log-transformed data. The sponsor successfully responded to all deficiencies. Subject 5 had nonzero predose chlorthalidone levels in both periods which is most likely due to an interfering substance. There were statistically significant sequence effects for chlorthalidone AUC_{0-t}, C_{max}, and their log-transformed values which is removed if Subject 5 is deleted.

DISSOLUTION: Dissolution testing acceptable for both strengths.

PRIMARY REVIEWER: James D. Henderson **BRANCH:** II

INITIAL: /S/ **DATE** 2-5-93

BRANCH CHIEF: Nhan L. Tran, Ph.D **BRANCH:** II

INITIAL: /S/ **DATE** 3/10/93

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Shrikant V. Dighe, Ph.D

INITIAL /S/ **DATE** 3/2/93

DIRECTOR, OFFICE OF GENERIC DRUGS: Roger L. Williams, M.D.

INITIAL: /S/ **DATE** 5/25/93

ANDA 74-107

Sidmak Laboratories, Inc.
Attention: Satish P. Patel
17 West Street
P.O. BOX 371
East Hanover, NJ 07936

JUL 11 1997

Dear Sir:

This is in reference to our correspondence of May 7,1997, stating the dissolution testing requirements for Atenolol and Chlorthalidone Tablets USP. This supersedes our letter of May 7, 1997.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than (b)4(Q) of the labeled amount of Atenolol and (b)4(Q) Chlorthalidone in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

(b)4 - Confidential Business

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 2 4 1997

Atenolol and Chlorthalidone
Tablet, USP, 50 mg/25 mg
100 mg/25 mg
ANDA # 74-107
Reviewer: Man M. Kochhar
74107DW.996

Sidmak Laboratories, Inc.
East Hanover, NJ
Submission Date:
September 26, 1996

An Amendment to the Review of Dissolution Data and a Waiver Request

The firm has changed the supplier for their atenolol in the manufacture of atenolol and chlorthalidone Tablets 50 mg/25 mg and 100 mg/25.

The firm has submitted comparative dissolution data in support of a request for a bioequivalence study waiver on its test product as provided for under 21 CFR 320.22. The listed drug product is Tenoretic 100, (Atenolol and Chlorthalidone, 100 mg/25 mg) manufactured by Zeneca Pharmaceuticals, Inc.

The application was incomplete because the firm did not provide the dissolution on their 50 mg/25 mg tablets of atenolol and chlorthalidone.

Comments:

1. The Sponsor has changed the source for their atenolol from [redacted](b)4 - [redacted] to [redacted](b)4 - [redacted]. The formulation of the new product is same as of the approved product on which an acceptable bioequivalence study was conducted.

2. Dosage, strength, labeling and the indications for use for the test product are identical to those of the reference product Tenoretic.

3. The USP dissolution method was used. The dissolution testing data demonstrate that the bio batch, new test batch and reference products meet the dissolution specifications (Table 1).

4. The dissolution testing on 100 mg/25 mg atenolol/chlorthalidone is acceptable and the waiver of in vivo bioequivalence study should be granted on this strength based upon 21 CFR 320.22.

5. The sponsor has provided the dissolution on atenolol/chlorthalidone 100 mg/25 mg but the dissolution on atenolol/chlorthalidone 50 mg/25 mg is not required by the Division of Bioequivalence.

6. The formulation of the test product for both strengths is given in Table 2.

Recommendations:

1. The sponsor has provided the dissolution on their Atenolol/Chlorthalidone 100 mg/25 mg tablet which is acceptable to the division of Bioequivalence.

2. The Division of Bioequivalence agrees that the information submitted by Sidmak Pharmaceuticals, Inc. on its drug products, Atenolol:Chlorthalidone 100 mg/25 mg and 50 mg/25 mg tablets fall under 21 CFR 320.22 of the Bioavailability/Bioequivalence Regulations. The waivers of in vivo bioequivalence study for both strengths are granted. From the bioequivalence point of view, the Division of Bioequivalence deems Atenolol:Chlorthalidone tablets, USP, 100 mg/25 mg and 50 mg/25 mg to be bioequivalent to the bio-batch Atenolol:Chlorthalidone (Tenoretic 100 and Tenoretic 50 tablets) manufactured by Zeneca Pharmaceuticals.

3. The dissolution testing conducted by Sidmak Pharmaceuticals on its drug product, Atenolol:Chlorthalidone 100 mg:25 mg (lot #94-018T) has been found acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP XXIII apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than (b)(4)(Q) of the labeled amount of Atenolol and [redacted](Q) Chlorthalidone in the dosage form is dissolved in 45 minutes.

The firm should be informed of the recommendations.

TABLE 1

IN VITRO DISSOLUTION TESTING

Drug: Atenolol:Chlorthalidone; 100 mg/25 mg
ANDA # 74-107
Firm: Sidmak Pharmaceuticals, Inc.

Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of water
Specifications: (b)4 (Q) of Atenolol and (b)4 (Q) Chlorthalidone in 45 minutes
Assay Methodology: (b)4

Results:

Sampling Time	Test Product Lot # 90-018T			Reference Product Lot # 90-026T(Bio-Batch)		
Minutes	**Atenolol**			**Atenolol**		
	Mean	Range	St Dev	Mean	Range	St Dev
15	93.0	(b)4 - Confidential Business	4.8	93.9	(b)4 - Confidential	2.7
30	95.0		2.2	96.3		1.9
45	97.0		1.8	97.8		1.5
	Chlorthalidone			**Chlorthalidone**		
15	96.0	(b)4 - Confidential Business	5.8	100.6	(b)4 - Confidential	4.7
30	98.0		2.1	101.9		1.9
45	100.0		1.9	102.9		1.8

	Reference(Tenoretic) Lot # DA291		
	Atenolol		
15	94.0	(b)4 - Confidenti	2.2
30	97.0		4.9
45	100.0		2.3
	Chlorthalidone		
15	76.0	(b)4 - Confidential Business	3.1
30	82.0		4.9
45	86.0		2.8

DJ

APR 30 [illegible]

Atenolol and Chlorthalidone
Tablet, USP, 50 mg/25 mg
100 mg/25 mg
ANDA # 74-107
Reviewer: Man M. Kochhar
74107DW.996

Sidmak Laboratories, Inc.
East Hanover, NJ
Submission Date:
September 26, 1996

Review of Dissolution Data and a Waiver Request

The firm has changed the supplier for their atenolol in the manufacture of atenolol and chlorthalidone Tablets 50 mg/25 mg and 100 mg/25.

The firm has submitted comparative dissolution data in support of a request for a bioequivalence study waiver on its test product as provided for under 21 CFR 320.22. The listed drug product is Tenoretic 100, (Atenolol and Chlorthalidone, 100 mg/25 mg) manufactured by Zeneca Pharmaceuticals, Inc.

Comments:

1. The Sponsor has changed the source for their atenolol from [redacted](b)4 - [redacted] to [redacted](b)4 - [redacted] The formulation of the new product is same as of the approved product on which an acceptable bioequivalence study was conducted.

2. Dosage, strength, labeling and the indications for use for the test product are identical to those of the reference product Tenoretic.

3. The USP dissolution method was used. The dissolution testing data demonstrate that the bio batch, new test batch and reference products meet the dissolution specifications (Table 1).

4. The dissolution testing on 100 mg/25 mg atenolol/chlorthalidone is acceptable and the waiver of in vivo bioequivalence study should be granted on this strength based upon 21 CFR 320.22.

5. The sponsor has provided the dissolution on atenolol/chlorthalidone 100 mg/25 mg but the dissolution on atenolol/chlorthalidone 50 mg/25 mg is not provided.

6. The formulation of the test product for both strengths is given in Table 2.

Recommendations:

1. The sponsor has not provided the dissolution on their Atenolol/Chlorthalidone 50 mg/25 mg tablet and therefore, the application is incomplete.

2. The Division of Bioequivalence agrees that the information submitted by Sidmak Pharmaceuticals, Inc. on its drug products, Atenolol:Chlorthalidone 100 mg/25 mg tablets fall under 21 CFR 320.22 of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for this strength is granted. From the bioequivalence point of view, the Division of Bioequivalence deems Atenolol:Chlorthalidone tablets, USP, 100 mg/25 mg to be bioequivalent to the bio-batch Atenolol:Chlorthalidone (Tenoretic 100 tablets) manufactured by Zeneca Pharmaceuticals.

3. The dissolution testing conducted by Sidmak Pharmaceuticals on its drug product, Atenolol:Chlorthalidone 100 mg:25 mg (lot #94-018T) has been found acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP XXIII apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than (b)4 (Q) of the labeled amount of Atenolol and [redacted] (Q) of the labeled amount of Chlorthalidone in the dosage form is dissolved in 45 minutes.

The firm should be informed of the recommendations.

From bioequivalence standpoint, the application is incomplete.

TABLE 1

IN VITRO DISSOLUTION TESTING

Drug: Atenolol:Chlorthalidone; 100 mg/25 mg
ANDA # 74-107
Firm: Sidmak Pharmaceuticals, Inc.

Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of water
Specifications: (b)4 of Atenolol and (b)4 (Q)
Chlorthalidone in 45 minutes
Assay Methodology: (b)4 -

Results:

Sampling Time	Test Product Lot # 90-018T			Reference Product Lot # 90-026T(Bio-Batch)		
Minutes	**Atenolol**			**Atenolol**		
	Mean	Range	St Dev	Mean	Range	St Dev
15	93.0	(b)4 -	4.8	93.9	(b)4 -	2.7
30	95.0		2.2	96.3		1.9
45	97.0	onfidenti	1.8	97.8	onfidenti	1.5
	Chlorthalidone			**Chlorthalidone**		
15	96.0	(b)4 -	5.8	100.6	(b)4 -	4.7
30	98.0	Confidentia	2.1	101.9	Confidentia	1.9
45	100.0		1.9	102.9		1.8
	Test L0t # 90-018T			Reference(Tenoretic) Lot # DA291		
	Atenolol			**Atenolol**		
15	93.0	(b)4 -	4.8	94.0	(b)4 -	2.2
30	95.0	onfidenti	2.2	97.0	Confidentia	4.9
45	97.0		1.8	100.0	Business	2.3
	Chlorthalidone			**Chlorthalidone**		
15	96.0	(b)4 -	5.8	76.0	(b)4 -	3.1
30	98.0	onfidenti	2.1	82.0	onfidenti	4.9
45	100.0		1.9	86.0		2.8

TABLE 2

FORMULATION

Ingredients	100 mg Tablet Mg/tablet	50 mg Tablet Mg/tablet
Atenolol, USP	100.00	50.00
Chlorthalidone, USP	25.00	25.00
Corn Starch NF	(b)4 - Confidential Business	
Starch Pregelatinized, NF		
Sodium Lauryl Sulfate NF		
Povidone USP K-30		
Purified Water, USP[1]		
Microcrystalline Cellulose, NF		
Sodium Starch Glycolate, NF		
Silicon Dioxide, NF		
Magnesium Stearate, NF		
TOTAL WEIGHT	265.00	145.00

[1] Does not appear in the finished product.